

Serial No. 08/944,850
Filed: October 6, 1997

REMARKS

Claim Status

Claims 39-48 remain in this application. Claims 39-41, 43, 44 and 46 have been amended.

Information Disclosure Statement:

This issue was addressed separately in the "SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT" filed on May 31, 2001.

Claim Objections:

Claims 41, 43 and 44 are objected to.

The Examiner states that "elements" of dependent claim 41 and "sensor elements" of dependent claims 43 and 44 are presumed to find their antecedent basis in the first and second sensor elements of independent claim 39.

Claims 41, 43 and 44 have been amended to address the Examiner's objection. The amended form, "said first and second sensor elements," clearly finds the antecedent basis in the independent claim 39.

Accordingly, Applicants respectfully request the Examiner to withdraw this objection.

Rejection under 35 U.S.C. § 112, 2d paragraph:

Claims 39-48 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that the "text "at least" in clause (i) of the providing step (a) of sole independent claim 39 is indefinite, as it is unclear whether the presence of any other subpopulation is a necessary element of the method, despite the presence of a second in clause (ii), especially since another subpopulation is not referred to again in claims 39 and 41-48."

Claim 39 has been amended and the text "at least" has been deleted.

Accordingly, Applicants respectfully request the Examiner to withdraw this rejection.

Rejection under 35 U.S.C. § 102:

Claims 39, 40, 43-45, 47 and 48 are rejected under 35 U.S.C. § 102(e) as being

anticipated by Pinkel *et al.* (US005690894A).

The Examiner states that "Pinkel *et al.* discloses an assay method corresponding to the disclosed apparatus (Fig. 4) which comprises a sensor array **14** having at least two subpopulations (the groups of strands **10**) of different sensor elements." The Examiner further states that the assay method disclosed in Pinkel *et al.* comprises "measuring first fluorescent signals (column 13, lines 33-39) of at least two of the sensor elements **11** of the first subpopulation (group) with detector **20**, and summing the first fluorescent signals (column 9, lines 12-14 and 21-25)." Applicants respectfully traverse.

Pinkel *et al.* is directed to the fabrication and use of biosensors comprising a plurality of optical fibers where each fiber has biological "binding partners" attached to its "sensor end". In column 9, lines 12-14 and 21-25 (the section referred to by the Examiner) discloses alternative ways of measuring the signal generated by the biosensor, which are "to measure the aggregate signal provided by the entire transmission face 15 of the biosensor" or "to read the signal from single optical fibers 10 or from groups of optical fibers where all of the optical fibers 10 in a group bear the same species of biological binding partner." Essentially, this suggests taking a single reading of either a single fiber or a group of fibers. Pinkel *et al.* does not teach or suggest to take individual reading of individual fibers (or even groups of fibers) and summing them together. That is, the "aggregate signal" measured from the "entire transmission face" does not equal the sum of individual signals within a group of optical fibers. Therefore, the reference does not disclose a method of measuring and summing individual signals from single optical fibers within a group.

In contrast, claim 39 in the amended form is directed to a method comprising measuring a first and a second fluorescent signal from a first and a second of the first sensor elements, respectively, and summing the first and second fluorescent signals.

As the Examiner is aware, anticipation under 35 U.S.C. § 102 requires that "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990).

Applicants submit that not every element of the method in claim 39 is identically shown in Pinkel *et al.* for the reasons outlined above. That is, the reference does not teach a method of measuring and summing individual signals from individual sensor elements of a subpopulation.

Applicants note that “a claim in a dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.” 35 U.S.C. §112, fourth paragraph. Thus, Pinkel *et al.* does not anticipate the dependent claims of claim 39, which includes claims 40, 43-45, 47 and 48.

Accordingly, Applicants respectfully request the Examiner to withdraw this rejection.

Rejection under 35 U.S.C. § 103:

Claim 46 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Pinkel *et al.* (US005690894A).

As discussed above, Pinkel *et al.* is directed to the fabrication and use of biosensors comprising a plurality of optical fibers each fiber having attached to its “sensor end” biological “binding partners,” but it does not disclose a method of measuring and summing individual signals from single optical fibers within a group.

Claim 46 in the present application is dependent on claim 39, and is directed to an assay method comprising measuring a first and a second fluorescent signal from a first and a second of the first sensor elements, respectively, adjusting the baseline of said first and second fluorescent signals and then summing said first and second fluorescent signals.

As argued above, a *prima facie* case of obviousness requires that “there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. M.P.E.P. §2143.

The Examiner states that “it would have been obvious to one of ordinary skill in the art at the time the invention was made to adjust the baseline of fluorescence signals in the method of Pinkel *et al.* because the detector system may be employed with a computerized data acquisition system and analytical program (column 12, lines 10-22) and such an adjustment (calibration) is a known and useful step in accurately measuring responses.”

Pinkel *et al.* does not motivate a skilled artisan to practice the claimed invention, i.e., to adjust the baseline of each individual signal generated from an individual sensor element within a subpopulation of sensor elements. As noted above, Pinkel *et al.* teaches that the signal is read “from groups of optical fibers where all of the optical fibers 10 in a group bear the same species of biological binding partner.” But the reference is silent with respect to measuring individual signals from individual optical fibers in a group, which is an important and technically difficult step, further away from baseline-adjusting individual signals from individual optical fibers in a group.

Therefore, a *prima facie* case of obviousness has not been made against claim 46. Accordingly, Applicants respectfully request the Examiner to withdraw this rejection.

Claims 41 and 42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Pinkel *et al.* (US005690894A) in view of Lough *et al.* (US005900481A).

Pinkel *et al.* is discussed above.

Lough *et al.* teaches compositions comprised of at least one bead conjugated to a solid support and further conjugated to at least one nucleic acid and methods for making such compositions.

Claims 41 and 42 are dependent on claim 39, which are directed to an assay method comprising measuring a first and a second fluorescent signal from a first and a second sensor element, respectively, within a subpopulation of sensor elements, said sensor elements comprising beads distributed in wells, and summing said first and second fluorescent signals.

As argued above, a *prima facie* case of obviousness requires that the references provide the motivation to practice the invention.

The Examiner states that “[t]he beads are of Lough *et al.* are suitable for the types of binding molecules used and fluorescent signals measured in the sensor array 14 of Pinkel *et al.* and further provide the convex surface Pinkel *et al.* identifies as advantageous.” The Examiner further states that “it would have been obvious to one of ordinary skill in the art at the time of the invention was made to modify the method of Pinkel *et al.* to specify that the sensor ends therein

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were bound to beads as suggested by Lough *et al.* (as the fiber strands 10 in Pinkel *et al.*, qualify as a support as described by Lough *et al.* at column 3, line 29).” Applicants respectfully traverse.

As a first consideration, neither reference, taken alone or in combination, teach or suggest adding beads to the ends of the Pinkel *et al.* fibers, taking individual measurements of each bead/fiber sensor element and summing the signal with another signal from a different sensor element. Even assuming, arguendo, that the fiber strands of Pinkel “qualify as a support”, this is not sufficient to provide the necessary motivation. The Examiner is reminded that

the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. M.P.E.P. §2143.01.

Applicants further note that, as stated in MPEP § 2143.03, “[i]f an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is non-obvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).”

Finally, the references do not teach or suggest all the claim limitations, because they do not teach or suggest a method of measuring and summing individual fluorescent signals from individual fibers within a group.

Therefore, a *prima facie* case of obviousness has not been made against claim 39, hence claims 41 and 42. Accordingly, Applicants respectfully request the Examiner to withdraw this rejection.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned “**Version with markings to show changes made.**”

For the Examiner’s convenience, a clean copy of the currently pending claims is attached hereto.

Applicants submit that the claims are now in condition for allowance and an early notification of such is solicited. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

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Respectfully submitted,

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Version with Markings to Show Changes Made

In the specification:

Prior to the first sentence, please insert the following paragraph:

--This invention was made with government support under N00014-94-1-0312 awarded by the Department of the Navy, Office of Naval Research. The government has certain rights in the invention.--.

In the Claims:

Please amend the claims as follows:

39. An assay method comprising:

a) providing a sensor array comprising:

i) [at least] a first subpopulation comprising first sensor elements; and

ii) a second subpopulation comprising second sensor elements;

b) adding a sample comprising a first target analyte that binds to said first sensor elements;

c) measuring

i) a first fluorescent signal[s] of a first [at least two] of said first sensor elements [of said first subpopulation]; and

ii) a second fluorescent signal of a second of said first sensor elements; and

d) summing said first and second fluorescent signals.

40. A method according to claim 39 further comprising:

b) adding a sample comprising a second target analyte that binds to said second sensor elements;

c) measuring

i) a third [second] fluorescent signal[s] of a first [at least two] of said second sensor elements [of said second subpopulation]; and

ii) a fourth fluorescent signal of a second of said second sensor elements; and

d) summing said third and fourth [second] fluorescent signals.

41. A method according to claim 39 wherein said first and second sensor elements comprise beads.

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43. A method according to claim 39 wherein said first and second sensor elements comprise chemical functional groups.

44. A method according to claim 39 wherein said first and second sensor elements comprise oligonucleotides.

46. A method according to claim 39 wherein prior to said summing, the baseline of said first and second fluorescent signals are adjusted.

Appendix: Pending Claims

39. An assay method comprising:
- a) providing a sensor array comprising:
 - i) a first subpopulation comprising first sensor elements; and
 - ii) a second subpopulation comprising second sensor elements;
 - b) adding a sample comprising a first target analyte that binds to said first sensor elements;
 - c) measuring
 - i) a first fluorescent signal of a first of said first sensor elements; and
 - ii) a second fluorescent signal of a second of said first sensor elements; and
 - d) summing said first and second fluorescent signals.
40. A method according to claim 39 further comprising:
- b) adding a sample comprising a second target analyte that binds to said second sensor elements;
 - c) measuring
 - i) a third fluorescent signal of a first of said second sensor elements; and
 - ii) a fourth fluorescent signal of a second of said second sensor elements; and
 - d) summing said third and fourth fluorescent signals.
41. A method according to claim 39 wherein said first and second sensor elements comprise beads.
42. A method according to claim 39 wherein said sensor array comprises beads distributed in wells.
43. A method according to claim 39 wherein said first and second sensor elements comprise chemical functional groups.
44. A method according to claim 39 wherein said first and second sensor elements comprise oligonucleotides.
45. A method according to claim 39 wherein said first target analyte is an oligonucleotide.
46. A method according to claim 39 wherein prior to said summing, the baseline of said first and second fluorescent signals are adjusted.

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47. A method according to claim 39 wherein the signal-to-noise ratio is increased as a result of said summing.

48. A method according to claim 39 wherein said sensor array comprises a fiber optic bundle.